

a hydrogen atom or a C<sub>sub</sub>.1-6 alkyl group; or R<sub>sup</sub>.1 and R<sub>sup</sub>.2, together represent an alkylene chain -(CH<sub>sub</sub>.2)<sub>sub</sub>.n-, where n represents 1, 2 or 3;

one of the groups represented by R<sub>sup</sub>.5, R<sub>sup</sub>.6 and R<sub>sup</sub>.7 is a hydrogen atom or a C<sub>sub</sub>.1-6 alkyl, C<sub>sub</sub>.3-7 cycloalkyl, C<sub>sub</sub>.3-6 alkenyl, phenyl or phenyl-C<sub>sub</sub>.1-3 alkyl group, and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C<sub>sub</sub>.1-6 alkyl group;

G represents a hydrogen atom or a halogen atom or a hydroxy, C<sub>sub</sub>.1-4 alkoxy, phenyl-C<sub>sub</sub>.1-3 alkoxy or C<sub>sub</sub>.1-6 alkyl group or a group -NR<sub>sup</sub>.10 R<sub>sup</sub>.11 or -CONR<sub>sup</sub>.10 R<sub>sup</sub>.11 (wherein R<sub>sup</sub>.10 and R<sub>sup</sub>.11, which may be the same or different, each represents a hydrogen atom or a C<sub>sub</sub>.1-4 alkyl or C<sub>sub</sub>.3-6 alkenyl group, or together with the nitrogen atom to which they are attached form a saturated 5 to 7 membered ring);

and physiologically acceptable salts and solvates thereof.

The compounds are potent and selective antagonists of the effect of 5-HT and 5-HT<sub>2</sub>LE.

Solubility modulated drug delivery system

#### ABSTRACT:

A drug delivery device for the controlled release of a therapeutically active ingredient into an environment of use is disclosed which comprises:

- (A) a core composition comprising
  - (a) a plurality of controlled release solubility modulating units comprising solubility modulating agents each of which is a complexing agent or a surfactant and which is either (i) surrounded by a water insoluble cast containing at least one pore forming additive dispersed throughout said cast, or (ii) dispersed in an inorganic matrix and (iii) 0.1 to 75% by weight, based on the total weight of (i) and (ii), of at least one water leachable pore forming additive dispersed throughout said unit.

US-CI-CURRENT: 424/472, 462

US PAT NO: 4,939,144 IMAGE AVAILABLE- LS: 5 of 25  
TITLE: Tricyclic ketone derivatives as 5-HT antagonists

#### ABSTRACT:

The invention relates to ketones of the general formula (I):

wherein Im represents an isobutyl group of the formula: #BSTR2es one of the groups represented by R<sub>sub</sub>.1, R<sub>sub</sub>.2 and R<sub>sub</sub>.3 is a hydrogen atom or a C<sub>sub</sub>.1-6 alkyl, C<sub>sub</sub>.3-7 cycloalkyl, C<sub>sub</sub>.1-6 alkenyl, phenyl or phenyl-C<sub>sub</sub>.1-3 alkyl group, and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C<sub>sub</sub>.1-6 alkyl group;

n represents 1, 2 or 3;

G represents a hydrogen atom, a halogen atom, or a hydroxy, C<sub>sub</sub>.1-4 alkoxy, phenyl-C<sub>sub</sub>.1-3 alkoxy or C<sub>sub</sub>.1-6 alkyl group, or a group -NR<sub>sup</sub>.4 R<sub>sup</sub>.5 or -CONR<sub>sup</sub>.4 R<sub>sup</sub>.5, (wherein R<sub>sup</sub>.4 and R<sub>sup</sub>.5, which may be the same or different, each represents a hydrogen atom or a C<sub>sub</sub>.1-4 alkyl or C<sub>sub</sub>.3-6 alkenyl group, or together with sup.6, wherein R<sub>sup</sub>.6 represents a hydrogen atom or a group selected from C<sub>sub</sub>.1-10 alkyl, C<sub>sub</sub>.3-6 alkenyl, C<sub>sub</sub>.3-10 alkenyl, C<sub>sub</sub>.3-7 cycloalkyl, C<sub>sub</sub>.3-7 cycloalkyl, C<sub>sub</sub>.1-4 alkyl, phenyl, phenyl-C<sub>sub</sub>.1-3 alkyl, -OR<sub>sup</sub>.7, -OR<sub>sup</sub>.7, -CONR<sub>sup</sub>.7 R<sub>sup</sub>.8 or -SO<sub>sub</sub>.2 R<sub>sup</sub>.7 (wherein R<sub>sup</sub>.7 and R<sub>sup</sub>.8, which may be the same or different, each represents a hydrogen atom, a C<sub>sub</sub>.1-6 alkyl, or C<sub>sub</sub>.3-7 cycloalkyl group, or a phenyl or phenyl-C<sub>sub</sub>.1-3 alkyl group, in which the phenyl group is optionally substituted by one or more C<sub>sub</sub>.1-4 alkyl, C<sub>sub</sub>.1-4 alkoxy or hydroxy groups or halogen atoms, with the proviso that R<sub>sup</sub>.7 does not represent a hydrogen atom when R<sub>sup</sub>.8 represents a group -OR<sub>sup</sub>.7); and physiologically acceptable salts and solvates thereof.

The compounds are potent and selective antagonists of the effect of 5-HT and 5-HT<sub>2</sub> receptors and are useful, for example, in the treatment of

604/87011 group of the formula: ~~wherein~~ the various substituents are defined hereinbelow. The compounds are potent and selective antagonists of the effect of 5-HT at 5-HT<sub>2</sub> receptors and are useful, for example, in the treatment of psychotic disorders, anxiety, and nausea and vomiting.  
US-CL-CURRENT: 540/603; 546/200; 548/136

US PAT NO: 4,822,791 LS: 12 of 26  
TITLE: Pharmaceutical compositions  
of 2,2-1,1-(bis-2,2'-(3,1-benzoxazin-4-one)9 ethylenes

ABSTRACT:

This invention relates to pharmaceutical compositions of compounds of the general formula: ~~wherein~~ wherein R<sub>sup.1</sub> is an aryl group or a substituted aryl group wherein the substituent is halogen, hydroxy, C<sub>sub.1-6</sub> lower alkoxy, C<sub>sub.1-6</sub> lower alkylendioxy, halo C<sub>sub.1-6</sub> lower alkyl, cyano, nitro, mono- or di-C<sub>sub.1-6</sub> alkylazino or C<sub>sub.1-6</sub> lower alkanoylamino; or a 5-membered or 6-membered C<sub>sub.1-6</sub> alkyl substituted or unsubstituted heterocyclic group containing a heteroatom selected from oxygen, nitrogen, and sulfur, or a condensed heterocyclic group consisting of a heterocycle as defined above and a benzene nucleus, and R<sub>sup.2</sub> and R<sub>sup.2'</sub> are, independently, hydrogen, halogen, nitro, C<sub>sub.1-6</sub> lower alkyl or C<sub>sub.1-6</sub> lower alkoxy. These compounds have been found to exhibit hyaluronidase inhibiting activity, ant4,814,183 LS: 13 of 26

TITLE: Device for the controlled release of drugs with  
Donnan-like modulation by charged insoluble resins

ABSTRACT:

The instant invention is directed to a drug delivery device for the controlled release of beneficial agents and drugs into an environment of use comprising:

- (A) a core composition comprising
  - (a) a water insoluble, non-diffusible charged resin entity, and
  - (b) a diffusible, water soluble ionizable therapeutically active ingredient carrying the same charge as said resin entity; and
- (B) a substantially impermeable water-insoluble wall surrounding said core composition, prepared from a semipermeable material substantially impermeable to the core composition and permeable to the passage of an external fluid in the environment of use, with said wall having a hole(s) for release of the therapeutic agent through the water insoluble wall.

US-CL-CURRENT: 424/485, 443, 444, 486, 487, 488

US PAT NO: 4,806,581 LS: 14 of 26  
TITLE: Imidazoyl- indolylpropanones as 5-HT<sub>2</sub> receptor  
antagonists

ABSTRACT:

The invention relates to compounds of the effect of 5-HT at 5-HT<sub>2</sub> receptors and are useful, for example, in the treatment of psychotic disorders, anxiety, and nausea and vomiting.

US-CL-CURRENT: 514/212, 322, 397; 540/803; 546/201; 548/136

US PAT NO: 4,795,844 LS: 15 of 26  
TITLE: Device for pH independent release of drugs through the  
Donnan-like influence of charged insoluble resins

ABSTRACT:

A device is disclosed for the controlled delivery of a beneficial agent. The agent is delivered to the environment surrounding the device at a substantially constant rate for a specified period with a reduced dependence on the environmental pH. The device is comprised of a core compartment containing (1) a charged, water insoluble, non-diffusible component and (2) at least beneficial agent(s). In operation the insoluble charged component (1) and the beneficial agent(s) (2) are released into the environment.

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have the same electro-static charge and do not form an ion exchange complex. Rather, a Donnan influenced mass transport phenomena of the beneficial agent is effected through the pores in the device, actuated by water from the environment, with migration of the freely mobile diffusible species (beneficial agent) away from the non-mobile species (charged entity). This effects the release of the beneficial agent through the wall at a controlled rate with reduced pH dependency.  
US-1-CURRENT: 424/468, 457, 474, 482

US PAT NO: 4,785,122

LS: 16 of 26

TITLE: Method for production of amine compound

## ABSTRACT:

A method for the producing 2-[[[5-(dialkylaminolalkyl)-2-furanyl-methyl]-thio]-ethane amine by the reaction of cysteamine or cysteamine hydrochloride containing free hydrogen chloride with 5-(dialkyl aminolalkyl) furfuryl alcohols, which method can be obtained the product in a highly yield by carrying out said reaction at a temperature in the range of 30 degrees pharmaceutical preparation which is prepared as a pharmaceutical preparation comprising lower alkyl ether of cellulose, polyacrylic acid or its pharmaceutically acceptable salt, and active drugs, or a pharmaceutical preparation comprising lower alkyl ether of cellulose, polyacrylic acid or its pharmaceutically acceptable salt, and active drugs together with a foaming agent, so that it may release the active drugs by such slow degrees in the stomach or the intestinal tract as to make it possible to provide an adequate supply of active drugs in enough concentration to display their therapeutic value for many hours.  
US-CL-CURRENT: 424/44, 51, 487, 488

US PAT NO: 4,755,579

LS: 18 of 26

TITLE: Fluoroalkoxy substituted benzimidazoles useful as gastric acid secretion inhibitors

## ABSTRACT:

Dialkoxypyridines of formula I ##STR1## wherein R1 is 1-3C-alkyl which is completely or predominantly substituted by fluorine, or a chlorodifluoromethyl radical and R1' is hydrogen, halo, trifluoromethyl, 1-3C-alkyl, or 1-3C-alkoxy which is optionally completely or predominantly substituted by fluorine, or R1 and R1', together with the oxygen atom to which R1 is bonded, are 1-2C-alkylenedioxy, which is optionally completely or partly substituted by fluorine, or chlorotrifluoroethylenedioxy, R3 is 1-3C-alkoxy, one of R2 and R4 is 1-3C-alkoxy and the other is a hydrogen atom or 1-3C-alkyl and n is 0 or 1, and salts thereof are new compounds with a pronounced protective action on the stomach. Processes for preparing these compounds, medicaments: Pharmaceutical composition [(1,2,-dioxo-1,3-propanediyl)diimino-bisbenzoic acid derivatives and their use

## ABSTRACT:

Compounds of the general formula: ##STR1## wherein A and B are both hydrogen, or one of A and B is a group (G) of the formula: ##STR2## and the other is a group R<sub>sup.5</sub> wherein R<sub>sup.1</sub> is an aryl group or a heterocyclic group, both of them being optionally substituted, and R<sub>sup.4</sub> and R<sub>sup.5</sub> are both hydrogen or together form a single chemical bond, R<sub>sup.2</sub> and R<sub>sup.3</sub> are both hydrogen, and, where applicable, pharmaceutically acceptable salts thereof are hyaluronidase inhibitors, and useful as anti-allergic agent and anti-ulcerous agent. Among the compound (II), those wherein one of A and B is the group (G) and the other is the group R<sub>sup.3</sub> wherein R<sub>sup.4</sub> and R<sub>sup.5</sub> together form a single chemical bond, R<sub>sup.1</sub> is

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R<sup>1</sup> and R<sup>2</sup> are independently carboxy or its functional derivative other than methyl ester, are novel.

US-CL-CURRENT: 214,211, 218, 227.5, 230.5, 237.8, 255, 331, 357, 365, 381, 394, 400, 415, 427, 438, 452, 466, 471, 485, 486, 522, 533, 563

US PAT NO: 4,686,230 L5: 20 of 26  
TITLE: Picoline derivative useful as gastric acid secretion inhibitors

ABSTRACT:

Picoline derivatives of the formula I ##STR1## wherein the substituents have the meanings given in the description, and their salts are new compounds having a pronounced protective action on the lining membrane of the stomach are described by the invention. The compounds are prepared from and contains precipitated and undried magaldrate gel, a polyhydric ##alcohol## and fluidizing amounts of a first and second fluidizer. One fluidizer is provided by an aluminum hydroxide gel having colloidal properties and the second by a pharmaceutically acceptable citrate ion source including citric acid. The process and composition are characterized in providing rehydratable antacid composition which when admixed with water forms a fluid, resuspendible, pharmaceutically elegant suspension possessing high antacid capacity and ##stability## at even elevated magaldrate concentrations in addition to the ability to fluidize stiff, paste-like magaldrate gel cakes.

US-CL-CURRENT: 424/689, 690

US PAT NO: 4,634,777 L5: 22 of 26  
TITLE: ((1,3-dioxo-1,2-propanediyl)diiminol)-bistenoic acid derivatives

ABSTRACT:

Compounds of the general formula: ##STR1## wherein A and B are both hydrogen, or one of A and B is a group (G) of the formula: ##STR2## and the other is a group R, or, lower alkyl or lower alkoxy, and R<sup>1</sup> and R<sup>2</sup> are independently carboxy or its functional derivative, with the proviso that (a) when A and B are both hydrogen,

then R<sup>1</sup> and R<sup>2</sup> cannot be both hydrogen, and, where applicable, pharmaceutically acceptable salts thereof are hyaluronidase inhibitors, and useful as anti-allergic agents and anti-inflammatory agents. Among the compounds ##STR3## there is also one of 3

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and R.sub.5 together form a single chemical bond, R.sub.1 is unsubstituted aryl and R.sub.2 and/or 4, 253, 325, 342, 495; 549/77, 362, 441, 496; 556/420; 560/21, 27, 37, 45, 47, 48; 562/435, 442, 453, 455, 456, 457; 564/153

US PAT NO: 4,590,192 LS: 23 of 26  
TITLE: Benzisothiazoles, their pharmaceutical compositions, and method of use

ABSTRACT:

Compounds of formula (I), or a pharmaceutically acceptable salt, quaternized derivative, N-oxide or solvate thereof:

R.sub.1—Ar—(CH.sub.2).sub.a—X—(CH.sub.2).sub.b—N1—Het (I)  
wherein: the substituents are defined in the specification.  
The compounds are useful in treating excess gastric acid secretions such as peptic ulcers.

US-CURRENT: 514/233.8, 321, 373; he oral mucosa, (2) a water-soluble protein, (3) a polyhydric alcohol, and (4) a fatty acid ester or/and a carboxyvinyl polymer, has various advantages such as good feeling in use, good retainability within the mouth, slow release, improved absorbability of drug through the mucosa, improved bioavailability, etc., and therefore can be used an excellent pharmaceutical preparation for administration to the mucous membrane of the mouth.

US-CURRENT: 424/435, 81; 514/773, 774, 775

US PAT NO: 4,558,044 LS: 25 of 26  
TITLE: 1,2,4-Benzothiadiazines

ABSTRACT:

Disclosed are compounds of the formula

R.sub.1—Ar—(CH.sub.2).sub.a—X—(CH.sub.2).sub.b—N1—Het  
wherein R.sub.1 is guanidino or substituted guanidino, Ar is furandyl, thiophendyl, phenylene, p-pounds are useful for the treatment or prophylaxis of disorders relating to excess gastric acid secretion in mammals.

US-CURRENT: 514/223.2, 222.8; 544/12, 13

US PAT NO: 4,432,983 LS: 26 of 26  
TITLE: Conformationally restricted histamine H.sub.2-receptor antagonists containing a tropane ring

ABSTRACT:

Histamine H<sub>2</sub> role, isothiazole, oxazole, isoxazole, triazole, thiadiazole, benzimidazole, or furan ring either unsubstituted or substituted with a C.sub.1—C.sub.4 alkyl, hydroxyl, trifluoromethyl, benzyl, halogen, amino, or dimethylaminomethyl group are disclosed along with a synthetic method of producing such compounds and their use as gastric-acid-production inhibitors.

US-CURRENT: 514/304, 927; 544/224, 333, 405; 546/125

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L1 220 S RANITIDINE  
 L2 0 S ALCOHOL OR ETHANOL  
 L3 184400 S ALCOHOL OR ETHANOL OR 2-PROPANOL  
 L4 192 S L1 AND L3  
 L5 26 S L4 AND STABILITY  
 L6 24 S L5 AND ORAL

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US PAT NO: 4,968,507 [IMAGE AVAILABLE-] LS: 1 of 26  
 TITLE: Controlled porosity osmotic pump

ABSTRACT:

The instant invention is directed to an osmotic pump comprising:  
 (A) at least one active agent surrounded by  
 (B) a rate controlling water insoluble wall, having a fluid permeability of 6.96.times.10.sup.-18 to 6.96.times.10.sup.-14 cm.sup.3 sec/g and a reflection coefficient of less than 1, prepared from:  
 (i) a polymer permeable to water but impermeable to solute and  
 (ii) 0.1 to 60% by weight, based on the total weight of (i) and (ii), of at least one pH insensitive pore forming additive dispersed throughout said wall.

US-CL-CURRENT: 424/465, 473; 604/890.1, 892.1

US PAT NO: 4,963,546 [IMAGE AVAILABLE-] LS: 2 of 26  
 TITLE: Ketone derivatives which are antagonists of 5-HT at 5-HT.sub.3 receptors, compositions containing them, and method of use

ABSTRACT:

The invention relates to compounds of the general formula (I): ##STR1## wherein R.sup.1 and R.sup.2 together form a C.sub.3-5 alkylene chain and R.sup.3 is a hydrogen atom; or R.sup.1 and R.sup.3 together form a C.sub.2-4 alkylene chain and R.sup.2 is a hydrogen atom; A-B represents the group R.sup.4 R.sup.5 C-CH.sub.2 or R.sup.4 C.dbd.CH; R.sup.4 and R.sup.5, which may be the same or different, each represent a hydrogen atom or a C.sub.1-6 alkyl group; and Im represents an imidazolyl group of formula: ##STR2## wherein one of the groups represented by R.sup.6, R.sup.7 and R.sup.8 is a hydrogen atom or a C.sub.1-6 alkyl, C.sub.3-7 cycloalkyl, C.sub.3-6 alkenyl, phenyl or phenylC.sub.1-3 alkyl group and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C.sub.1-6 alkyl group; and physiologically acceptable salts and solvates thereof. The compounds are potent and selective antagonists of the effect of 5-HT at 5-HT.sub.3 receptors and are useful, for example in the treatment of psychotic disorders, anxiety, and nausea and vomiting.

US-CL-CURRENT: 514/214, 296, 411; 540/581; 546/94; 548/428

US PAT NO: 4,950,681 [IMAGE AVAILABLE-] LS: 3 of 26  
 TITLE: Ketone derivatives

ABSTRACT:

The invention relates to ketones of the general formula (I): ##STR1## wherein R.sup.1 represents a hydrogen atom or a group selected from C.sub.1-6 alkyl, C.sub.3-6 alkenyl, C.sub.3-10 alkynyl, C.sub.3-7 cycloalkyl, C.sub.3-7 cycloalkylC.sub.1-4 alkyl, phenyl or phenylC.sub.1-4 alkyl in which the phenyl group is optionally substituted by one or more C.sub.1-4 alkyl, C.sub.1-4 alkoxy or hydroxy groups or halogen atoms, with the proviso that R.sup.3 does not represent a hydrogen atom when R.sup.1 represents a group -CO.sub.2 R.sup.8 or -SO.sub.2 R.sup.8; R.sup.2 represents a hydrogen atom or a C.sub.1-6 alkyl, C.sub.3-6 alkenyl, C.sub.3-7 cycloalkyl, phenyl or phenylC.sub.1-3 alkyl group; R.sup.3 and R.sup.4, which may be the same or different, each represents

**G 000226**

I. [45] Date of Patent: Nov. 26, 1991

[54] **AQUEOUS RANITIDINE COMPOSITIONS  
STABILIZED WITH ETHANOL**

[75] Inventor: David R. Long, Royston, England

[73] Assignee: Glaxo Group Limited, London,  
England

[21] Appl. No.: 494,804

[22] Filed: Mar. 14, 1990

**Related U.S. Application Data**

[63] Continuation of Ser. No. 344,620, Apr. 28, 1989, abandoned, which is a continuation of Ser. No. 131,442, Dec. 11, 1987, abandoned.

[30] **Foreign Application Priority Data**

Dec. 12, 1986 [GB] United Kingdom ..... 86 29781

[51] Int. Cl.<sup>5</sup> ..... A61K 31/34

[52] U.S. Cl. .... 514/471

[58] Field of Search ..... 514/461, 471

[56] **References Cited**

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*Primary Examiner*—Frederick E. Waddell

*Assistant Examiner*—Diane Gardner

*Attorney, Agent, or Firm*—Bacon & Thomas

[57] **ABSTRACT**

The stability of aqueous formulations of ranitidine or a physiologically acceptable salt thereof is enhanced by the addition of ethanol.

12 Claims, No Drawings

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# 1 **AQUEOUS RANITIDINE COMPOSITIONS STABILIZED WITH ETHANOL**

This application is a continuation of application Ser. No. 07/344,620, filed Apr. 28, 1989, now abandoned, which is a continuation of Ser. No. 07/131,442, filed Dec. 11, 1987, now abandoned.

The present invention relates to a pharmaceutical composition containing as active ingredient the histamine H<sub>2</sub> antagonist ranitidine.

Ranitidine, [N-[2-[[[5-(dimethylamino)methyl-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine, and its physiologically acceptable salts are described in British Patent Specification No. 1565966. In that specification there is reference to liquid formulations for oral and parenteral administrations and there is a description of an aqueous based formulation for intravenous use and another of an oral syrup. Both of these formulations contained sufficient hydrochloric acid to achieve a pH of 5.0 and the syrups also contained Sorbitol solution BPC and a flavour as required.

British Patent Application No. GB 2142820A describes aqueous based formulations containing ranitidine and/or one or more of its physiologically acceptable salts thereof having a pH within the range 6.5-7.5. In that specification there is reference to liquid formulations for oral and parenteral administration and there are examples of aqueous formulations for intravenous and oral use. These formulations contain ranitidine hydrochloride and are buffered to a pH of approximately 7 and for intravenous administration the formulations also contain phenol or sodium chloride. For oral administration the formulation also contains hydroxypropylmethyl cellulose as a viscosity enhancing agent, a preservative (parabens), a sweetening agent and a flavour. These compositions have a significantly greater shelf-life over those in British Patent No. 1565966.

We have now surprisingly found that the stability of ranitidine in aqueous based formulations and more particularly aqueous based formulations for oral administration may be substantially enhanced by the addition of ethanol to the formulation.

Thus the present invention provides a pharmaceutical composition which is an aqueous formulation of ranitidine and/or one or more physiologically acceptable salts thereof also containing ethanol. The aqueous formulation is prepared using ingredients of a purity such that it is suitable for administration to patients and will in general contain at least one conventional pharmaceutical excipient in addition to the ethanol and ranitidine and/or physiologically acceptable salts thereof.

The amount of ethanol present in the formulation is such that the resulting formulation has the enhanced stability. Preferably the amount of ethanol in the composition on a weight/volume basis of the complete formulation, is within the range 2.5% to 10%, and more particularly is between 5 to 10% w/v, more especially 7-8% w/v.

Preferred compositions according to the invention are those in which the pH of the aqueous formulation is within the range 6.5 to 7.5, particularly 6.8 to 7.4 and more especially 7 to 7.3. The required pH of the formulation is preferably obtained by the use of suitable buffer salts for example, potassium dihydrogen orthophosphate and disodium hydrogen orthophosphate or citric acid and disodium hydrogen orthophosphate.

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A preferred embodiment of the invention is an aqueous formulation for oral administration. Such a formulation may comprise ranitidine and/or one or more of its physiologically acceptable salts dissolved in water, ethanol, a preservative and a viscosity enhancing agent. Preferably the required pH of the formulation is obtained by the use of appropriate buffer salts. Optionally the composition may also contain other conventional excipients such as a sweetener, a flavour and/or flavouring aids.

Examples of suitable preservatives include one or more alkyl hydroxybenzoates such as methyl, ethyl, propyl and/or butyl hydroxybenzoates.

Examples of suitable viscosity enhancing agents include Xanthan gum, sorbitol glycerol, sucrose or a cellulose derivative such as carboxymethylcellulose or a salt thereof of a C<sub>1-4</sub> alkyl and/or a hydroxy-C<sub>1-4</sub> alkyl ether of cellulose such as methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxyethylmethylcellulose and hydroxypropylmethylcellulose.

Examples of suitable sweeteners include saccharin sodium, sodium cyclamate, sorbitol and sucrose.

Examples of suitable flavouring agents include 'mint' flavours such as peppermint flavouring agents.

The concentration of ranitidine in the oral formulation, expressed as free base, is conveniently within the range 20-400 mg per 10 ml, for example 20-200 mg per 10 ml, more particularly 150 mg per 10 ml dose.

The amount of ethanol in the formulation for oral administration, expressed as a percentage of the complete formulation on a weight/volume basis, is preferably within the range 2.5 to 10%, and more particularly between 5 to 10%, more especially 7-8%.

The amount of viscosity enhancing agent in the formulation will preferably be sufficient to give a solution with a viscosity in the range of 10 to 100 centipoises.

The aqueous formulations for oral administration are conveniently prepared by mixing an aqueous solution of ranitidine and/or one or more of its physiologically acceptable salts together with ethanol and the excipients, with aqueous solution or dispersion of the viscosity enhancing agent.

The aqueous formulations according to the invention are preferably prepared using ranitidine in the form of its hydrochloride salt.

An illustrative example of a formulation according to the invention is as follows. In this example the relative proportions of ranitidine hydrochloride and the buffer salts are such that the formulation has a pH of approximately 7.

Ranitidine oral liquid formulation (150 mg/10 ml)  
expressed as free base

	% w/v
Ranitidine hydrochloride	1.68
Ethanol	7.5
Potassium dihydrogen orthophosphate	0.095
Disodium hydrogen orthophosphate anhydrous	0.350
Hydroxypropylmethylcellulose	qs
Preservative	qs
Sweetening agents	qs
Flavour	qs
Purified water BP to	100 ml

I claim:

1. A pharmaceutical composition which is an aqueous formulation for oral administration of an effective

5,068,249

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amount of ranitidine and/or one or more physiologically acceptable salts thereof, said formulation comprising a stabilizing effective amount of ethanol and said composition having a pH in the range of 6.5-7.5.

2. A pharmaceutical composition according to claim 1 containing 2.5% to 10% weight/volume ethanol based on the complete formulation.

3. A pharmaceutical composition according to claim 1 containing 7% to 8% weight/volume ethanol based on the complete formulation.

4. A pharmaceutical composition according to claim 1 having a pH in the range 6.8 to 7.4.

5. A pharmaceutical composition according to claim 1 having a pH in the range 7.0 to 7.3.

6. A pharmaceutical composition according to claim 1 wherein said pH is obtained by the use of buffer salts.

7. A pharmaceutical composition according to claim 1 prepared using ranitidine in the form of the hydrochloride salt.

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8. A pharmaceutical composition as claimed in claim 1, wherein the effective amount is 20-400 mg ranitidine per 10 ml dose expressed as free base.

9. A pharmaceutical composition as claimed in claim 1, wherein the effective amount is 20-200 mg ranitidine per 10 ml dose expressed as free base.

10. A pharmaceutical composition as claimed in claim 1, wherein the effective amount is 150 mg ranitidine per 10 ml dose expressed as free base.

11. A pharmaceutical composition which is an aqueous formulation of ranitidine suitable for oral administration containing 150 mg ranitidine per 10 ml dose expressed as free base, said formulation having a pH in the range 7.0 to 7.3 and also containing 7% to 8% weight/volume ethanol based on the complete formulation.

12. A pharmaceutical composition according to claim 11 wherein said pH is obtained by the use of buffer salts.

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SYMBOLS

- ✓ Rejected
- Allowed
- (Through comment) Considered
- Withdrawn
- △ Non-abstract
- △ Non-abstract
- △ Appeal
- △ Rejected

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SEARCHED			
Class	Sub.	Date	Exmr.
514	461	6/12/87	W
		↓ 11/11/87	W

INTERFERENCE SEARCHED			
Class	Sub.	Date	Exmr.

SEARCH NOTES		
Cos on large (Parent)	Date	Exmr.
Pat. 13/442-120	6/12/87	W

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1.	Application	papers.	
2.	Oral Amdt A		4-28-89
3.	RBms		June 28, 89 4/21
4.	Reg Time gtd.	1ms.	Oct. 30, 1989
5.	Amitt B - Priv Act		Oct. 30, 1989
6.	FR3ms		Nov. 14, 1989 11/3
7.	Reg Time gtd.	1ms.	Nov. 14, 1990
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SYMBOLS

..... Request

..... Answer

..... (Through answers) Discovery

..... Deposition

..... Affidavit

..... Interrogatory

..... Reply

..... Motion

SEARCHED			
Class	Sub.	Date	Exmr.
514	461	4/29/00	
514	471	5/29/91	DG

SEARCH NOTES		
	Date	Exmr.
Cas on line Parents	4/29/00	
parents	12/6/90	DG
APS	12/6/90	DG

INTERFERENCE SEARCHED			
Class	Sub.	Date	Exmr.
514	471	5/29/91	DG

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1. Application _____ papers.	
2. <i>Grant C</i>	<i>May 14, 1990</i>
3. <i>Rejected 3 mos.</i>	<i>04 MAY 1990 4/30</i>
4. <i>Reg Time 9th 3 mos.</i>	<i>Oct. 31, 1990</i>
5. <i>Grant D</i>	<i>Oct. 31, 1990</i>
6. <i>Price Out Statement (comp)</i>	<i>Oct. 31, 1990</i>
7. <i>Disclosure Statement</i>	<i>1-10-91</i>
8. <i>3 mos rejection</i>	<i>1/22/91</i>
9. <i>Reg Time 6th</i>	<i>May 10, 1991</i>
10. <i>Reg Recon. + Decler.</i>	<i>May 10, 1991</i>
11. <i>Grant C</i>	<i>June 3, 1991</i>
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